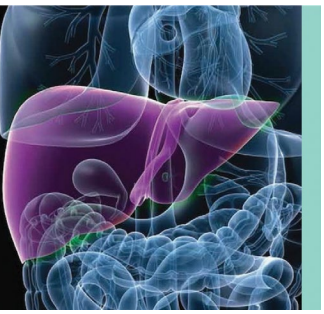

Diagnostic and Treatment Dilemmas in Pediatric NAFLD

Bryan Rudolph, M.D., M.P.H., F.A.A.P.

Nonalcoholic fatty liver disease (NAFLD) encapsulates two distinct conditions: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Both are defined histologically by the presence of macrovesicular hepatic steatosis, while NASH is also characterized by the additional features of inflammation and ballooning degeneration.

NAFLD is the most common liver disease in the United States and among the leading causes of cirrhosis and liver transplantation in adults.[1] Although these outcomes are rare in pediatric populations, NAFLD affects up to 10% of all US children and is progressive.[2] Diagnosing and treating pediatric NAFLD may therefore be a critical means of addressing this growing public health problem.

Based on expert opinion, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommends screening for NAFLD between 9 and 11 years of age with alanine aminotransferase (ALT) levels in obese children or in overweight children with additional risk factors.[2] This differs from the American Association for the Study of Liver Diseases Practice Guidance, which does not recommend screening in children because of a paucity of data.[1] In contrast, there are no recent screening guidelines from the American Academy of Pediatrics. In short, consistent guidelines and additional data are needed to improve NAFLD screening and diagnosis among children.

In children with persistent ALT elevation, available guidelines recommend ruling out other causes of liver disease, such as autoimmune hepatitis and Wilson's disease, among others.[2] This is uncommon in routine pediatric practice, however.[3] Moreover, testing is complicated and difficult to interpret. Autoimmune antibodies, for example, are often falsely elevated and necessitate a liver biopsy when strongly positive or when the liver kidney microsomal antibody is (at all) positive.[1]

Biopsy should also be considered in children with a negative workup but persistent ALT elevation and an increased risk for NASH and/or advanced fibrosis (i.e., ALT ≥ 80 U/L).[2] However, because ALT values fluctuate and may be normal, risk stratification based on ALT alone is insufficient and may be improved by considering other risk factors, such as older age; obesity (versus overweight children);

Abbreviations: ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

From the Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY.

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increased waist circumference; Hispanic ethnicity (particularly if from Central and South America); comorbidities, such as diabetes, panhypopituitarism, or obstructive sleep apnea; high-fructose consumption; and high gamma-glutamyltransferase (GGT) level.[2,4] Risk factors such as intestinal dysbiosis and genetics almost certainly play a critical role in development of NAFLD but are not clinically used for diagnosis or risk stratification at this time.[4]

Although relatively safe, biopsy is invasive and limited by sampling bias and interpreter variability. Moreover, histological staging with the NAFLD Activity Score (NAS) may be less useful in young children.[5] Whereas adults have lobular inflammation, ballooning degeneration, and perisinusoidal fibrosis (termed type 1 NASH), young children often present with portal inflammation, little to no ballooning degeneration, and portal fibrosis (termed type 2 NASH). The etiology, significance, and progression risk of type 2 or pediatric NASH are unknown. Nevertheless, the NAS inadequately captures these unique histological findings in young children and creates challenges when used as an inclusion criterion or outcome in pediatric drug trials.

Despite these limitations, biopsy remains the gold standard diagnostic test in children largely because of a paucity of noninvasive testing data. For example, there are no pediatric-specific data on common serological panels, such as the Fibrosis-4 index, NAFLD fibrosis score, and the Enhanced Liver Fibrosis (ELF) score panel. Similarly, ultrasound-based elastography tests (e.g., FibroScan) are poorly studied in pediatric NAFLD-specific cohorts. Some studies, mostly from Europe and with very few Hispanic patients, have shown comparable diagnostic ability with adults but may not be generalizable to US children.[4] Alternatively, several small US studies have shown magnetic resonance elastography to be efficacious, but it is more costly and may be limited by the need for sedation.[4] Noninvasive testing should therefore be used and interpreted thoughtfully.

Other clinical challenges vis-à-vis testing remain. For one, hepatic steatosis may be incidentally identified on imaging in a child with normal ALT. Although a reasonable approach is to repeat liver tests in 3 to 6 months or to diagnose subclinical NAFL and provide lifestyle counseling, no standard approach exists. Similarly, additional pediatric data are needed to understand the prevalence of "lean" NAFLD and when the benefits to biopsy outweigh risks.

Healthy eating and increased physical activity (i.e., lifestyle management) are the most efficacious treatments for fatty liver disease. However, the amount of weight loss that correlates with biochemical or histological improvement in children is unknown, and some only need to maintain their weight as they grow taller, decreasing body mass index slowly over time. Nevertheless, lifestyle management is challenging to implement and sustain for most families. Success may be aided by multidisciplinary lifestyle support, such as a dietician or behavioral therapist, but these services are not widely accessible and often are not covered by insurance. Social determinants of health may further inhibit access to such services and adherence to recommendations.

In a recent, sentinel study of 40 adolescent boys randomized to one of two arms, a chef-prepared, isocaloric, low added sugar diet (intervention) or a regular diet, those in the intervention group had more than a 6% decrease in hepatic fat after 8 weeks.[6] Furthermore, those in the intervention group also had a significant decrease in ALT, GGT, aspartate aminotransferase level, fasting glucose, total cholesterol, and low-density lipoprotein cholesterol. Although further study is required to confirm these findings, a low added sugar diet should currently be considered the primary treatment recommendation for children with NAFLD.

This recommendation is important because medications are not recommended for the treatment of pediatric NAFLD per NASPGHAN guidelines.[2] With that said, 800 IU vitamin E was associated with NASH resolution among children with ballooning degeneration in a large, multicenter, randomized placebo-controlled trial (TONIC study).[7] Although histological improvement was only a secondary endpoint in TONIC, many clinicians use vitamin E anyway for nondiabetic children with biopsy-proven NASH (and ballooning) given the lack of alternative options and documented efficacy of vitamin E in adults. Such practices could change, of course, if any of the multiple medications in adult phase 3 studies become available, although no similar, late-stage clinical trials are currently open in pediatric populations. Future research should therefore focus on novel therapies in children, in addition to the noninvasive testing methods described earlier.

CORRESPONDENCE

Bryan Rudolph M.D., M.P.H., F.A.A.P., Children's Hospital at Montefiore, Albert Einstein College of Medicine, 3411 Wayne Ave, 7th Floor, Bronx, NY 10467. E-mail: brudolph@montefiore.org

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